UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

April 23, 1999

MEMORANDUM

SUBJECT: Response to Comments Received to EPA's January 1999 Preliminary Risk Assessment for Propetamphos. Chemical Number 113601. DP Barcode D254788.

FROM: Steven A. Knizner, Branch Senior Scientist
Reregistration Branch 3
Health Effects Division (7509C)

TO: Christina Scheltema, Chemical Review Manager
Reregistration Branch 3
Special Review and Registration Division (7508C)

Responses to the HED Propetamphos Preliminary Risk Assessment, which was updated last on January 13, 1999, were received from the Natural Resources Defense Council (NRDC) and Wellmark, Inc, the registrant. The comments received were summarized in your memo dated March 25, 1999. Below please find your summation of comments and HED's response.

Comments from NRDC:

1. The risk characterization for toddlers exposed to propetamphos is inconsistent between the body of the risk assessment and the executive summary. Estimated propetamphos exposures to toddlers (based on residential SOPs) are 960 to >38,000 times higher than the NOAEL. The executive summary does not specify the magnitude of the exposure to toddlers, except for the lowest exposure scenario, post application inhalation exposure (termiticide use).

HED Response: The executive summary summarizes all post-application exposure estimates. It states that, "The post-application dermal **Margins of exposures (MOEs) were less than 1 for all [residential] scenarios addressed**. ***These exposure and risk estimates greatly exceed HED's level of concern."*** The individual MOEs for each of the exposure scenarios examined are contained in the body of the document.

policy is to use MOE calculations to express short and intermediate term risk estimates. The MOE is the NOAEL divided by the exposure estimate. This value is then compared to a safety factor, in the case of propetamphos 100. If the MOE is greater than 100, then the risk estimate does not exceed HED's level of concern. Conversely, if the MOE is less than 100, the risk estimate does exceed HED's level of concern. The commentors are expressing exposure estimates in terms of multiples of the NOAEL (divided by a 100 fold uncertainty factor).

2. Toddler inhalation exposure after propetamphos termiticide is injected into house foundation is calculated as 71X EPA's level of concern.

HED Response: The Multi-Chamber Concentration and Exposure Model (MCCEM), as outlined in the Standard Operating Procedures for Residential Exposure Assessments (12/18/97), was used to estimate post-application inhalation exposures for occupants, including toddlers. For toddlers, the inhalation MOE, calculated using the inhalation NOAEL, was 480.

3.a. Toddler dermal exposure estimate from treated carpet is 38,400X higher than the dermal NOAEL.

HED Response: policy is to use MOE calculations to express short and intermediate term risk estimates. The MOE is the NOAEL divided by the exposure estimate. The commentors are expressing exposure estimates in terms of multiples of the NOAEL (divided by an 100 fold uncertainty factor). Using the Residential SOPs, a MOE of 0.0026 was calculated. A MOE of greater than 100 would not exceed HED's level of concern.

4. Toddler dermal exposure estimate from treated carpet is more than 160X higher than the dermal NOAEL.

HED Response: policy is to use MOE calculations to express short and intermediate term risk estimates. The MOE is the NOAEL divided by the exposure estimate. The commentors are expressing exposure estimates in terms of multiples of the NOAEL (divided by an 100 fold uncertainty factor). Using a post-application exposure study (MRID #44319008), a dermal MOE of 1 was calculated. A MOE of greater than 100 would not exceed HED's level of concern.

5. Toddler hand-to-mouth exposure estimate from treated carpet or hard surface is 960X higher than the acute dietary NOAEL.

HED Response: policy is to use MOE calculations to express short and intermediate term risk estimates. The MOE is the NOAEL divided by the exposure estimate. The commentors are expressing exposure estimates in terms of multiples of the NOAEL (divided by an 100 fold uncertainty factor). Using the Residential SOPs, a MOE of 0.001 was calculated. A MOE of greater than 100 would not exceed HED's level of concern.

Comments from Wellmark:

1. NOEL is based on the NOEL for CheI instead of the overall NOEL and the relative CheI value (plasma, blood, brain, or liver) is not identified.

HED Response: The preliminary risk assessment contains only a summary of the toxicological studies used to establish endpoints and doses for risk assessments. A detailed description of these studies is found in the attached Hazard Identification Assessment Review Committee memorandum of May 27, 1998, which was provided as an attachment to the preliminary risk assessment. This document indicates whether plasma, red blood cell, and/or brain cholinesterase inhibition were used to establish the NOAEL, and supporting information available from other toxicological studies.

2. Assumption of 100% dermal absorption is not valid. Suggest using 23% dermal absorption value derived from ratio of acute oral and acute dermal LD50 values.

HED Response: This issue was recently examined by the HIARC on 2/24/99. The HIARC concluded that, "The 100% oral equivalent dermal absorption value is appropriate based on the comparison of LOAELs resulting from exposure to the technical product in the oral developmental toxicity study (8.0 mg/kg/day) and the 21-day dermal toxicity study (0.5 mg/kg/day) in rabbits based on a comparable endpoint (cholinesterase inhibition)." A full copy of the Committee report is attached.

3. Use of coveralls would not be expected to provide 50% reduction in dermal exposure because the areas of potential dermal exposure are already covered by PPE.

HED Response: As per HED policy, the addition of coveralls is assumed to result in 50% reduction in dermal exposure for the covered areas. The coveralls provide an extra layer of clothing through which any pesticide would have to migrate before reaching the skin.

Attachment: **MEMORANDUM** - ***"ORGANOPHOSPHATES: EVALUATION OF THE DERMAL ABSORPTION FACTOR*** - Report of the Hazard Identification Assessment Review Committee", B. Tarplee, February 24, 1999.

Attachment

HED DOC. NO. 013270

DATE: **February 24, 1999**

MEMORANDUM

SUBJECT: ***ORGANOPHOSPHATES: EVALUATION OF THE DERMAL ABSORPTION FACTOR*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Brenda Tarplee, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
And
Jess Rowland, Branch Chief
Reregistration Branch 3
Health Effects Division (7509C)

THROUGH: Mike Ioannou, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Pauline Wagner, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Margaret Stasikowski
Director
Health Effects Division (7509C)

On December 3, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of 16 organophosphates (bensulide, chlorethoxyphos, diazinon, ethoprop, ethyl parathion, fenamiphos, isofenphos, methyl parathion, methidathion, naled, phorate, phostebupirim, pirimiphos methyl, profenophos, propetamphos, and temephos) to determine the dermal absorption factor for use in occupational and/or residential dermal

exposure risk assessments. A dermal absorption value of 100%, the default value, had been previously assumed for these 16 organophosphates. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: Mike Ioannou, Pauline Wagner, David Anderson, William Burnam, Virginia Dobozy, Karen Hamernik, Pamela Hurley, Tina Levine, Nicole Paquette, Kathleen Raffaele, Jess Rowland, and PV Shah. Members in absentia: Sue Makris, and Nancy McCarroll.

Also in attendance were Anna Bearden, Christine Olinger, Clark Swentzel, Brenda Tarplee, and Robert Zendzian, HED.

Data Presentation:
and
Report Presentation

Jess Rowland
Chief, Reregistration Branch 3

And

Brenda Tarplee
Executive Secretary

I. INTRODUCTION

On December 3, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of 16 organophosphates (bensulide, chlorethoxyphos, diazinon, ethoprop, ethyl parathion, fenamiphos, isofenphos, methyl parathion, methidathion, naled, phorate, phostebupirim, pirimiphos methyl, profenophos, propetamphos, and temephos) for which the default value of 100% dermal absorption had been assumed for use in occupational and/or residential dermal exposure risk assessments. The HIARC objective at this meeting was to re-evaluate the toxicology data base to determine if a dermal absorption factor other than 100% could be determined for these 16 organophosphates.

II. BACKGROUND

Dermal absorption is a significant factor in occupational or residential risk assessments since exposures occur most frequently via the dermal route. Under the current toxicology data requirements, often data are not available to perform the route-specific risk assessment due to the lack of either dermal absorption data or appropriate dermal toxicity studies. One of the greatest difficulties encountered by the Committee is the task of estimating the proportion of the pesticide that is absorbed through the skin.

Dermal absorption is critical especially when the dose and endpoint selected for dermal risk assessment is from an oral study in which the experimental conditions (oral dosing) do not simulate the real-life exposure (dermal) scenario. Therefore, a correction must be made for this difference in absorption rates (i.e., oral vs. dermal). This can be accomplished by the use of a dermal absorption factor to adjust (correct) oral (systemic) absorption to potential dermal absorption.

For 15 organophosphates, an oral NOAEL was selected for dermal risk assessments which necessitated the use of a dermal absorption factor. However, because a dermal absorption study was not available for these organophosphates, the default value of 100% was assumed by HED's Toxicology Endpoint Selection Committee (TESC) or the HIARC.

When dermal absorption data were not available the Committee strived to estimate a dermal absorption value on a case-by-case basis by: 1) comparing the LOAELs established in the oral and dermal toxicity studies based on the same toxicological endpoint in the same species; 2) evaluating the physical or chemical properties of the pesticide (i.e., granular, emulsified concentrate, water solubility, etc.) and 3) the use of structure activity relationship (i.e., examining the similarity of the concerned pesticide to other chemicals or classes of chemical compounds).

To extrapolate a dermal absorption factor, the Committee evaluated the results of the following studies: 1) the maternal LOAEL from a developmental study in rats or rabbits to the LOAEL in a 21-day dermal toxicity study in the same species; and 2) the LOAEL from a 90- day feeding study in rats to that of the LOAEL established in the 90-day dermal study in rats. In addition, the Committee made a comparison of the acute oral and dermal LD_{50} values in the same species to gain some indication of dermal absorption. This comparison, however, is less reliable because of the ambiguous nature of the measurement. If an attempt was made to use the LD_{50} values, the dose levels used (i.e, not single dose or Limit-Dose studies), the vehicle used in both routes, and the nature of toxic response (other than death) were evaluated.. When a dermal absorption factor could not be estimated, the Committee assumed a 100% dermal absorption (which is likely an overestimate). The Committee was not able to estimate a dermal absorption factor because: 1) the appropriate oral and dermal studies in the same species were not available; 2) LOAELs were not established for both routes; 3) the toxicological endpoints were different via the oral and dermal routes; 4) no dermal absorption data on structurally related chemicals were available; and/or 5) there was low confidence in the data available for estimating a dermal absorption factor or in the estimation itself. In assuming the 100% dermal absorption value (default value), the Committee assumed absorption equivalency between oral and dermal routes.

III. EVALUATION OF INDIVIDUAL PESTICIDES

1. Bensulide

The 21-day dermal toxicity study in rats was not used since the principle toxicological endpoint of concern, cholinesterase inhibition, was not measured in this study. Therefore, oral values (doses) were selected for Short-, Intermediate and Long-term dermal risk assessments which necessitated a dermal absorption factor.

The Committee concluded that a 10% dermal absorption value is appropriate for bensulide. This decision is based upon the reevaluation of the oral and dermal data associated with the rat developmental study and the 21-day dermal toxicity study in rats. Comparisons of the results in the oral developmental toxicity (95 mg/kg/day based upon tremors and decreased body weight) and 21-day dermal toxicity studies (1000 mg/kg/day) in rats results in a 10% dermal absorption value.

2. Chlorethoxyphos

A dermal absorption factor is not necessary since a dermal dose (NOAEL) established in a 21-day dermal toxicity study in rats is available for Short-, Intermediate-, and Long-term dermal risk assessments.

3. Diazinon

A dermal absorption factor is required since oral values were selected for Short-, Intermediate-, and Long-term dermal risk assessments. The 100% oral equivalent dermal absorption value is appropriate based on the similarity of results (mortality) observed at the same dose (100 mg/kg/day) and in the same species (rabbits) via the oral (9/22 deaths in the developmental toxicity study) and dermal (4/5 deaths in the 21-day dermal toxicity study) routes.

4. Ethoprop

A comparison between oral and dermal toxicity studies in rabbits indicates a high degree of dermal absorption. Body weights were depressed at 1.0 mg/kg/day in the 21-day dermal toxicity study while there were no signs of maternal toxicity in the oral developmental toxicity study at the high dose of 2.5 mg/kg/day. Therefore, a value of 100% dermal absorption is appropriate.

5. Ethyl Parathion

A dermal absorption factor is required since oral values were selected for Short- and Intermediate-term dermal risk assessments (the use pattern does not indicate the need for Long-term dermal risk assessment).

The 100% oral equivalent dermal absorption value is appropriate based on the comparison of LD_{50} values obtained via the oral and dermal routes in several species as shown below:

Species	Route	LD_{50}
Mouse	Oral	5 mg/kg
	Dermal	19 mg/kg
Rat	Oral	3 mg/kg

	Dermal	6.8 mg/kg;
Rabbit	Oral	10 mg/kg
	Dermal	15 mg/kg
Guinea pig	Oral	8 mg/kg
	Dermal	45 mg/kg

NOTE: A 21-day dermal toxicity study, or any other dermal toxicity study, was not available for comparison with oral studies.

6. Fenamiphos

A dermal absorption factor is required since an oral value was selected for Long-term dermal risk assessment. Dermal values from a 21-day dermal toxicity study in rats were used for Short-and Intermediate-term dermal risk assessments and therefore, dermal absorption factors are not required for these assessments.

The 100% oral equivalent dermal absorption value is appropriate based on the maternal LOAEL established in the oral developmental toxicity study in rabbits (2.5 mg/kg/day; cholinergic signs) and the systemic LOAEL in the 21-day dermal toxicity study (2.5 mg/kg/day; cholinesterase inhibition) in the same species (rabbits).

7. Isofenphos

This organophosphate pesticide was canceled during the re-registration process.

8. Methidathion

A dermal absorption factor is required since oral values were selected for Short-, Intermediate-, and Long-term dermal risk assessments.

The comparison of the results from the oral and dermal studies yielded conflicting data. In the oral developmental toxicity study in rabbits, the LOAEL was 12 mg/kg/day, the highest dose tested, based on cholinergic signs. Dermal studies in rabbits produced conflicting results: one study in which the exposure was to the occluded skin, the LOAEL was 1 mg/kg/day based on mortality and cholinesterase inhibition; whereas, in another study in which exposure was to non-occlusive skin, the LOAEL was 20 mg/kg/day based on decreases in body weight gain and hypoactivity in one male. Comparison of the Acute Oral LD_{50} (46 mg/kg) and Dermal LD_{50} (1663 mg/kg) values in rats indicates dermal absorption to be approximately 3%. Comparison of the Acute Oral LD_{50} (80 mg/kg) and Dermal LD_{50} (640 mg/kg) values in rabbits indicates dermal absorption to be approximately 13%. Therefore, the Committee decided to retain the 100% dermal absorption factor pending re-evaluation of the dermal toxicity studies.

On 02/23/99 the HIARC evaluated the results of the two 21-dermal toxicity studies and discounted the 1987 study because the exposure was to the occluded skin which resulted in mortality and severe cholinesterase inhibition at the lowest dose tested. The Commmitte determined that the1986 study (non-occuluded) is appropriate for use in estimating a dermal absorption factor. The Committee concluded that a 60% dermal absorption value is appropriate for methidathion. This decision is based upon the reevaluation of the oral and dermal data associated with the rabbit developmental study and the 21-day dermal toxicity study in rabbits. Comparisons of LOAELs in the oral developmental toxicity (12 mg/kg/day, based on cholinergic signs) and 21-day dermal toxicity studies (20 mg/kg/day, based on decreased BW/BWG and hypoactivity in one male) in rabbits results in a 60% dermal absorption value. Cholinesterase inhibition was not measured in either study.

Although 60% may be somewhat of an overestimate of dermal absorption for the technical product, the physical/chemical properties of the technical (i.e., low melting point and good water solubility) would argue for moderate dermal absorption. It should be noted that the emulsifiable concentrate (EC) formulation is severely irritating to the skin which would greatly enhance absorption.

9. Methyl Parathion

A dermal absorption factor is required since oral values were selected for Short-, Intermediate-, and Long-term dermal risk assessments. The comparison of the results from the oral developmental and dermal toxicity studies in rats indicated a 100% dermal absorption value based on the LOAEL of 3 mg/kg/day in the rat oral developmental toxicity study and the LOAEL of 3.5 mg/kg/day in the rat two-week dermal neurotoxicity study (plasma, RBC, and brain cholinesterase inhibition in both studies).

The 100% oral equivalent dermal absorption value was also supported by the the comparison of the Acute Oral LD_{50} (4.5 mg/kg) and Dermal LD_{50} (6.0 mg/kg) values in rats.

10. Naled

A dermal absorption factor is necessary for Long-term dermal risk assessments due to the selection of an oral value from a rat study. Dermal values from a 28-day dermal toxicity study in rats were used for Short- and Intermediate-term dermal risk assessments and therefore, a dermal absorption factor is not required for these assessments.

The comparison of the results of the oral and dermal toxicity studies in rats indicated a 50% dermal absorption value based on the LOAEL of 10 mg/kg/day in the 28-day oral (gavage) and the LOAEL of 20 mg/kg/day in the 28-day dermal toxicity studies (neurotoxicity endpoints).

However, closer evaluation of the doses used in these studies (oral = 0, 0.25, 1.0, 10.0 or 100 mg/kg/day; and dermal = 0, 1, 20, or 80 mg/kg/day) indicate that the dose selection may have had an impact on the effect level in these studies. Following repeated oral dosing for 28 days, Naled at 10 mg/kg/day caused only mild cholinergic signs and 50% reduction in plasma and brain cholinesterase

inhibition; whereas via the dermal route at 20 mg/kg/day for the same duration (28 days), Naled produced more pronounced toxicity characterized as decreases in body weight gain as well as inhibition of plasma, red blood cell, and brain cholinesterase activity. Consequently, based on the dose/response curve, the Committee determined that the LOAEL in the dermal study could have actually been lower (comparable to the oral LOAEL) which would indicate the value of 100% to be appropriate (oral equivalent dermal absorption).

11. Phorate

A dermal absorption factor is required since oral values were selected for Short-, Intermediate-, and Long-term dermal risk assessment.

The 100% oral equivalent dermal absorption value is appropriate based on the comparison of the Acute Oral LD_{50} (2.7 mg/kg) and Dermal LD_{50} (3.0 mg/kg) values in rats.

12. Phostebupirim

A dermal absorption factor is required since oral values were selected for Short-, Intermediate-, and Long-term dermal risk assessments. A dermal absorption value of 100% is appropriate since comparison of the 21-day dermal toxicity study and the oral developmental toxicity study (both in rabbits) indicates high toxicity by both routes at very low dose levels (1 mg/kg/day or less).

13. Pirimiphos methyl

A dermal absorption factor is required since oral values were selected for Short-, Intermediate-, and Long-term dermal risk assessments. The Committee concluded that a 100% dermal absorption value is appropriate for pirimiphos-methyl. This decision is based upon the comparisons of LOAELs in the oral developmental toxicity (LOAEL = 24 mg/kg/day) and the 21-day dermal toxicity studies (LOAEL = 4 mg/kg/day) in rabbits based on the common endpoint (cholinesterase inhibition).

14. Profenophos

A dermal absorption factor is required since an oral value was selected for Long-term dermal risk assessment. Dermal values from a 21-day dermal toxicity study in rabbits were used for Short-and Intermediate-term dermal risk assessments and therefore, a dermal absorption factor is not required for these assessments.

Although the comparison of the Acute Oral LD_{50} (492 mg/kg) and Dermal LD_{50} (1610 mg/kg) values in rats indicates dermal absorption to be approximately 35%, there are no data available to support this estimate by comparison of LOAELs from oral and dermal toxicity studies. To account for this uncertainty, a dermal absorption value of 50% is assumed.

15. Propetamphos

A dermal absorption factor is required since oral values were selected for Short-, Intermediate-, and Long-term dermal risk assessments.

The 100% oral equivalent dermal absorption value is appropriate based on the comparison of LOAELs resulting from exposure to the technical product in the oral developmental toxicity study (8..0 mg/kg/day) and the 21-day dermal toxicity study (0.5 mg/kg/day) in rabbits based on a comparable endpoint (cholinesterase inhibition).

16. Temephos

A dermal absorption factor is required since oral values were selected for Short-, Intermediate-, and Long-term dermal risk assessments. The comparison of the results of the oral and dermal toxicity studies in rabbits was not possible since a LOAEL was not established in the oral study; in the dermal study, the LOAEL was 12.5 mg/kg/day. However, a dermal absorption study from the open literature (Army study) indicates a dermal absorption value of 38%. Therefore, this value (38%) was determined to be appropriate for this pesticide.

IV. CONCLUSION

Re-evaluation of the 100% default dermal absorption value for these 16 organophosphates resulted in: the use of a NOAEL from a 21-day dermal study for one pesticide (chlorethoxyphos); the reduction of the dermal absorption value to 50% for one pesticide (profenophos); the reduction of the dermal absorption value to 38% for one pesticide (temephos); the reduction of the dermal absorption value to 10% for one pesticide (bensulide); and the reaffirmation of the 100% dermal absorption value for the remaining 10 pesticides (no evaluation was made for isofenphos since the reregistration of this chemical has been canceled).

V. SUMMARY OF THE DERMAL ABSORPTION FACTORS

PESTICIDE	DERMAL ABSORPTION FACTOR	RATIONALE FOR THE DERMAL ABSORPTION FACTOR
Bensulide	**10%**	**Comparison of Oral / Dermal Rat Studies.**
Chlorethoxyphos	**Not Required**	**Use NOAEL from 21-Day Dermal Study in Rats.**
Diazinon	**100%**	**Comparison of Oral / Dermal Rabbit Studies.**
Ethoprop	**100%**	**Comparison of Oral / Dermal Rabbit Studies.**
Ethyl Parathion	**100%**	**No Dermal Studies Available for Comparison; Comparison of the Oral / Dermal LD_{50} Values in several species.**
Fenamiphos	**100%**	**Comparison of Oral / Dermal Rabbit Studies.**
Isofenphos	**Canceled**	**Canceled.**
Methidathion	**60%**	**Comparison of Oral / Dermal Rabbit Studies.**
Methyl parathion	**100%**	**Comparison of the Oral / Dermal Studies in Rats.**
Naled	**100%**	**Comparison of Oral / Dermal Rat Studies - However, 100% assumed since dose spacing indicates that LOAEL in the dermal study may be lower.**
Phorate	**100%**	**Comparison of the Oral / Dermal LD_{50} Values in Rats.**
Phostebupirim	**100%**	**Comparison of Oral / Dermal Rabbit Studies Indicates High Toxicity via Both Routes at Low Doses.**
Pirimiphos methyl	**100%**	**Comparison of Oral / Dermal Rabbit Studies.**
Profenophos	**50%**	**Comparison of the Oral / Dermal LD_{50} Values in Rats Indicate 35% - However, 50% assumed to account for uncertainty (no supporting studies).**
Propetamphos	**100%**	**Comparison of Oral / Dermal Rabbit Studies with Technical Products.**
Temephos	**38%**	**Dermal Absorption Study From the Open Literature.**